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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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☒ *Additional inventors are being named on the 2 0F 2 separately numbered sheets attached hereto.*

60/571788 U.S.PTO 22264 051704

TITLE OF THE INVENTION *(500 characters max)*

Chemical Compounds

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification	Number of Pages	34	☒ Claims	4
☐ Drawing(s)	Number of Sheets		☒ Abstract	1
☒ Application Data Sheet. See 37 CFR1.76		3		

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR1.27

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☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE Christine S. Lee DATE: 5/17/04

TYPED or PRINTED NAME Christine S. Lee REGISTRATION NO 42,788 *(if appropriate)*

TELEPHONE 860-686-2144 Docket Number. PC32041

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Additional Page

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Docket Number **PC32041**

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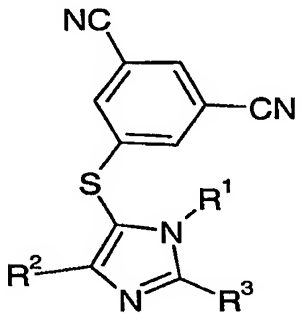
Chemical Compounds

This invention relates to isophthalonitrile derivatives, to their use in medicine, to compositions containing them, to processes for their preparation and to intermediates used in such processes.

The compounds of the present invention bind to the enzyme reverse transcriptase and are modulators, especially inhibitors thereof. Reverse transcriptase is implicated in the infectious lifecycle of HIV, and compounds which interfere with the function of this enzyme have shown utility in the treatment of conditions including AIDS. There is a constant need to provide new and better modulators, especially inhibitors, of HIV reverse transcriptase since the virus is able to mutate, becoming resistant to the effects of known modulators.

European patent application EP 0 786 455 A1 discloses a class of imidazole compounds which inhibit the growth of HIV. Antiviral activity is ascribed to a class of N(hydroxyethyl)pyrazole derivatives in US patent number 3,303,200. A number of pyrazoles are disclosed as reverse transcriptase inhibitors, including: a class of N-phenylpyrazoles (*J. Med. Chem.*, 2000, **43**, 1034); a class of C and S linked aryl pyrazoles (WO02/04424); and a class of O and S linked aryl pyrazoles, the O and S aryl link being adjacent to the nitrogen atom (WO02/30907).

According to the present invention there is provided a compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or derivative thereof, wherein:

R^1 is C $_{1-4}$ alkyl or C $_{3-6}$ cycloalkyl, wherein said alkyl is optionally substituted by pyridyl or pyridyl N-oxide;

R^2 is C $_{1-4}$ alkyl, C $_{3-6}$ cycloalkyl, or trifluoromethyl;

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R^3 is $-(CH_2)_mOH$, $-(CH_2)_mOC(O)NH_2$, $-(CH_2)_m NH_2$, or $-(CH_2)_m NHC(O)NH_2$; and m is 1, 2, 3 or 4.

The term "alkyl" as a group or part of a group includes straight chain and branched groups. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. The term "C_{3-6} cycloalkyl" means cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

In a further embodiment, R^1 is methyl, ethyl, i-propyl, cyclopropyl, or pyridylmethyl.

In yet a further embodiment, R^1 is methyl, ethyl or pyridylmethyl.

In yet a further embodiment, R^1 is methyl or ethyl.

In yet a further embodiment, R^1 is ethyl.

In yet a further embodiment, R^2 is methyl, ethyl, n-propyl, i-propyl, cyclopropyl, or trifluoromethyl.

In yet a further embodiment, R^2 is ethyl, i-propyl or cyclopropyl.

In yet a further embodiment, R^2 is ethyl

In yet a further embodiment, R^2 is i-propyl or cyclopropyl.

In yet a further embodiment, R^3 is $-(CH_2)_m OH$ or $-(CH_2)_m OC(O)NH_2$.

In yet a further embodiment , R^3 is $-CH_2OH$, $-(CH_2)_2 OH$, $-CH_2OC(O)NH_2$ or $-(CH_2)_2OC(O)NH_2$.

In yet a further embodiment , R^3 is $-CH_2OH$ or $-(CH_2)_2 OH$.

In yet a further embodiment , R^3 is $-(CH_2)_2OH$.

In yet a further embodiment , R^3 is $-(CH_2)_2OC(O)NH_2$.

It is to be understood that the invention covers all combinations of particular embodiments of the invention as described hereinabove, consistent with the definition of compounds of formula (I).

The compounds of the invention include compounds of formula (I) and pharmaceutically acceptable salts, solvates or derivatives thereof (wherein derivatives include complexes, polymorphs, prodrugs and isotopically-labeled compounds, as well as salts, solvates and salt solvates thereof), and isomers thereof. In a further embodiment, the compounds of the invention are the compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof, in particular the compounds of formula (I). It is to be understood that the aforementioned compounds of the invention include polymorphs and isomers thereof.

Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate,

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bicarbonate, bisulphate, borate, bromide, camsylate, carbonate, chloride, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrobromide, hydrochloride, hydroiodide, iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, sulphate, tartrate, tosylate and trifluoroacetate salts.

Hemisalts of acids may also be formed, for example, hemisulphate salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Pharmaceutically acceptable salts of compounds of formula (I) may be prepared by one or more of three methods:

(i) by reacting the compound of formula (I) with the desired acid;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid; or

(iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Complexes include clathrates, i.e. drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the pharmaceutical drug which contain two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially

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ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

The compounds of the present invention may have the ability to crystallize in more than one form, a characteristic known as polymorphism, and all such polymorphic forms ("polymorphs") are encompassed within the scope of the invention. Polymorphism generally can occur as a response to changes in temperature or pressure or both, and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics, and typically the x-ray diffraction patterns, solubility behavior, and melting point of the compound are used to distinguish polymorphs.

Certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include:

i) where the compound of formula I contains an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen of the alcohol functionality of the compound of formula I is replaced by (C_1-C_6)alkanoyloxymethyl; and

ii) where the compound of formula (I) contains a primary or secondary amino functionality (-NH_2 or –NHR where R ≠ H), an amide thereof, for example, replacement of one or both hydrogens with (C_1-C_{10})alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types in accordance with the invention may be found in the aforementioned references.

Moreover, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I).

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Also included within the scope of the invention are metabolites of compounds of formula (I), that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include:

(i) where the compound of formula (I) contains a methyl group, an hydroxymethyl derivative thereof ($-CH_3$ -> $-CH_2OH$);

(ii) where the compound of formula (I) contains a tertiary amino group, a secondary amino derivative thereof ($-NR^1R^2$ -> $-NHR^1$ or $-NHR^2$);

(iii) where the compound of formula (I) contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH); and

(iv) where the compound of formula (I) contains an amide group, a carboxylic acid derivative thereof ($-CONH_2$ -> COOH).

Compounds of formula I containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis/trans* (or Z/E) isomers are possible. Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula (I) containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all optical isomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, *d*-lactate or *l*-lysine, or racemic, for example, *dl*-tartrate or *dl*-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting

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diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994).

The present invention also includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

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Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Preferred compounds of formula (I) include the compounds: 5-{[1,4-diethyl-2-(2-hydroxyethyl)-1H-imidazol-5-yl]thio}isophthalonitrile; 5-{[4-ethyl-2-(2-hydroxyethyl)-1-(pyridin-2-ylmethyl)-1H-imidazol-5-yl]thio}isophthalonitrile; 5-{[4-ethyl-2-(2-hydroxyethyl)-1-methyl-1H-imidazol-5-yl]thio}isophthalonitrile; 2-{5-[(3,5-dicyanophenyl)thio]-4-ethyl-1-methyl-1H-imidazol-2-yl}ethyl carbamate; and pharmaceutically acceptable salts, solvates or derivatives thereof.

In the general processes, and schemes, that follow: R^1 to R^3 are as previously defined unless otherwise stated; X is halo, such as chloro, bromo or iodo; DMSO is dimethylsulphoxide; DMF is dimethylformamide.

Compounds of formula (I) may be prepared by any methods known for the preparation of compounds of analogous structure.

Compounds of formula (I), and intermediates thereto, may be prepared according to the schemes that follow.

It will be appreciated by those skilled in the art that certain of the procedures described in the schemes for the preparation of compounds of formula (I) or intermediates thereto may not be applicable to some of the possible substituents.

It will be further appreciated by those skilled in the art that it may be necessary or desirable to carry out the transformations described in the schemes in a different order from that described, or to modify one or more of the transformations, to provide the desired compound of formula (I).

It will be still further appreciated by those skilled in the art that, as illustrated in the schemes that follow, it may be necessary or desirable at any stage in the synthesis of compounds of formula (I) to protect one or more sensitive groups in the molecule so as to prevent undesirable side reactions. In particular, it may be necessary or desirable to protect amino or hydroxy groups. The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W Green

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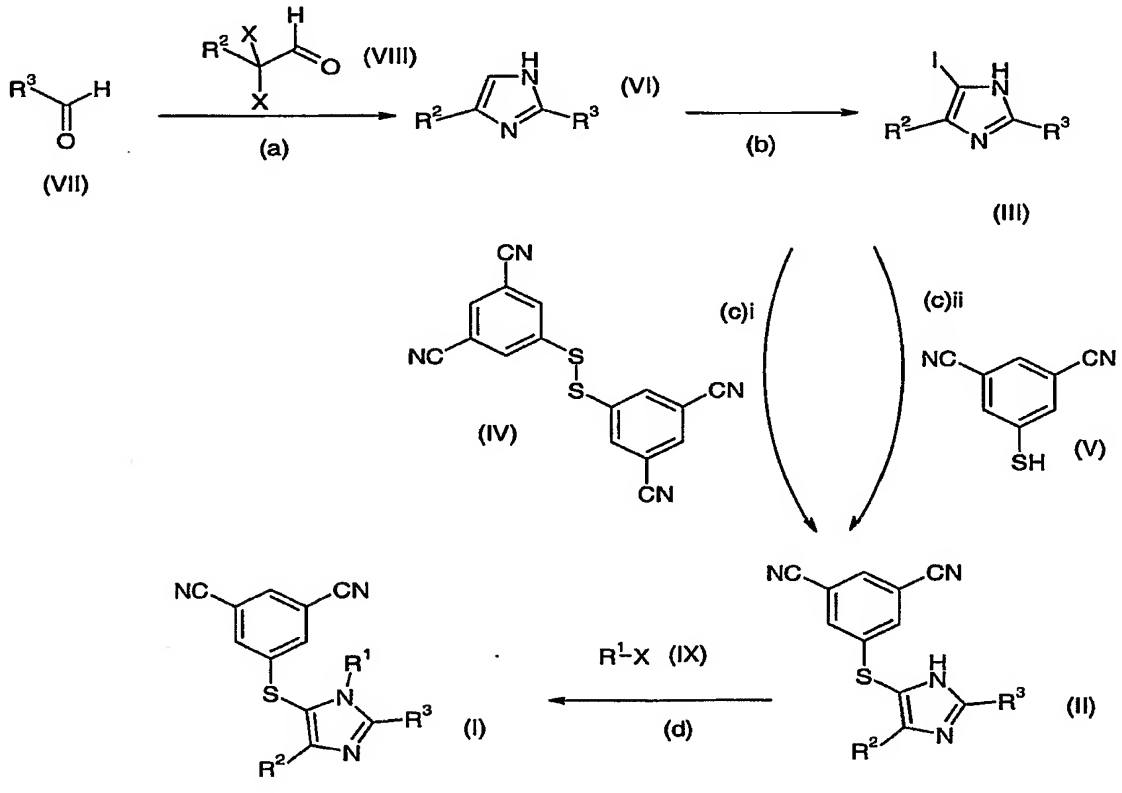
and Peter G M Wuts, third edition, (John Wiley and Sons, 1999), in particular chapter 2, pages 17-245 ("Protection for the Hydroxyl Group"), and chapter 7, pages 494-653 ("Protection for the Amino Group"), incorporated herein by reference, which also describes methods for the removal of such groups.

Scheme 1



With specific reference to scheme 1, the transformations depicted therein may be effected as follows:

(a) cyclisation

Compounds of formula (VI) may be prepared by the reaction of a compound of formula (VII) with a compound of formula (VIII) in the presence

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of a source of ammonia, such as concentrated ammonium hydroxide solution, 0.88 SG, under conventional conditions.

(b) iodination

Compounds of formula (III) may be prepared by the iodination of a compound of formula (VI) using a source of iodine, such as molecular iodine (e.g., iodine), or N-iodosuccinimide, under conventional conditions.

(c) nucleophilic substitution

(c)i In one embodiment of the present invention, compounds of formula (II) may be prepared by the reaction of compounds of formula (III) and the compound of formula (IV) under conventional conditions. Conveniently, the reaction may be effected using a base, such as an alkali metal base, for example, an alkali metal hydride (e.g., sodium, lithium or potassium hydride); in the presence of a solvent, such as a polar aprotic solvent (e.g., DMSO); and at ambient temperature.

(c)ii In a further embodiment, compounds of formula (II) may be prepared by the reaction of compounds of formula (III) and the compound of formula (V) under conventional conditions. Conveniently, the reaction may be effected using a base, such as an alkali metal base, for example, an alkali metal carbonate base (e.g., potassium, sodium or caesium carbonate); in the presence of a solvent, such as a polar aprotic solvent (e.g., acetonitrile) at ambient temperature or elevated temperature, such as ambient temperature to 100°C.

(d) alkylation

Compounds of formula (I) may be prepared by alkylating a compound of formula (II) with a compound of formula (IX) under conventional alkylating conditions. Conveniently, alkylation is effected using a base, such as an alkali metal base, for example, an alkali metal carbonate (e.g., sodium, potassium or caesium carbonate); in the presence of a solvent, such as a polar aprotic solvent (e.g., acetonitrile or DMF); and at ambient or elevated temperature, such as ambient temperature to 40°C.

Compounds of formulae (VII) and (VIII) are either known compounds or may be prepared by conventional chemistry. The compounds of formulae (IV) and (V) may be prepared as described in the preparations section below (respectively, preparations 6 and 3).

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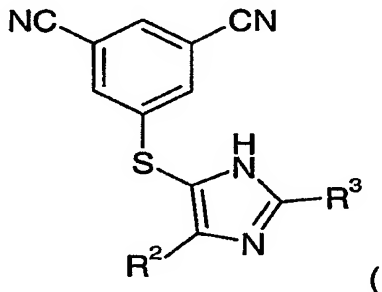
According to another aspect, the invention provides a process for preparing compounds of formula (I) comprising alkylation of a compound of formula (II)



(II)

with a compound of formula (IX).

Conveniently, alkylation is effected under the conditions described hereinabove in connection with scheme 1, step (d).

It will be appreciated by those skilled in the art that, in many cases, compounds of the formula (I) may be converted into other compounds of the formula (I) by functional group transformations.

The compounds of the invention are reverse transcriptase inhibitors and are therefore of use in the treatment of HIV, a retroviral infection genetically related to HIV, and AIDS.

Accordingly, in another aspect the invention provides a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof for use as a medicament.

In another aspect the invention provides a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof for use in the treatment of a HIV, a retroviral infection genetically related to HIV, or AIDS.

In another aspect the invention provides the use of a compound of the formula (I) or of a pharmaceutically acceptable salt, solvate or derivative thereof for the manufacture of a medicament for the treatment of a HIV, a retroviral infection genetically related to HIV, or AIDS.

In another aspect the invention provides a method of treatment of a mammal suffering from HIV, a retroviral infection genetically related to HIV, or AIDS which comprises treating said mammal with an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof.

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The compounds of the invention may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or in any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

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For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavours, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final

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formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of the invention used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified

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release of the compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound comprising, for example, ethanol (optionally, aqueous ethanol) or a suitable alternative agent for dispersing, solubilising, or extending release of the compound, the propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid

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processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-,
pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1µg to 10mg of the compound of the invention. The overall daily dose will typically be in the range 1µg to 200mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

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The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Inasmuch as it may desirable to administer a compound of the invention in combination with another therapeutic agent, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound of the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof,

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and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

For administration to human patients, having a weight of about 65 to 70kg, the total daily dose of a compound of the invention is typically in the range 1 to 10000mg, such as 10 to 1000mg, for example 25 to 500mg, depending, of course, on the mode of administration, the age, condition and weight of the patient, and will in any case be at the ultimate discretion of the physician. The total daily dose may be administered in single or divided doses.

Accordingly in another aspect the invention provides a pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

The compounds of formula (I) and their pharmaceutically acceptable salts, solvates and derivatives have the advantage that they are more selective, have a more rapid onset of action, are more potent, are better absorbed, are more stable, are more resistant to metabolism, have a reduced 'food effect', have an improved safety profile or have other more desirable properties (e.g. with respect to solubility or hygroscopicity) than the compounds of the prior art.

In particular, the compounds of formula (I) are more resistant to metabolism. In providing compounds of formula (I) which exhibit increased resistance to metabolism coupled with comparable or improved potency, the invention provides compounds which are therapeutically effective NNRTis at significantly lower dosages than the compounds of the prior art. Moreover, the increased solubility of compounds of formula (I) further facilitates lower dosages and flexibility in the routes of administration. These advantages can be expected to improve efficacy, safety, and patient compliance during treatment; and reduce the cost thereof.

The compounds of formula (I) and their pharmaceutically acceptable salts, solvates and derivatives may be administered alone or as part of a

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combination therapy. Thus included within the scope of the present invention are embodiments comprising coadministration of, and compositions which contain, in addition to a compound of the invention, one or more additional therapeutic agents. Such multiple drug regimens, often referred to as combination therapy, may be used in the treatment and prevention of infection by human immunodeficiency virus, HIV. The use of such combination therapy is especially pertinent with respect to the treatment and prevention of infection and multiplication of the human immunodeficiency virus, HIV, and related pathogenic retroviruses within a patient in need of treatment or one at risk of becoming such a patient. The ability of such retroviral pathogens to evolve within a relatively short period of time into strains resistant to any monotherapy which has been administered to said patient is well known in the literature. A recommended treatment for HIV is a combination drug treatment called **H**ighly **A**ctive **A**nti-**R**etroviral **T**herapy, or HAART. HAART combines three or more HIV drugs. Thus, the methods of treatment and pharmaceutical compositions of the present invention may employ a compound of the invention in the form of monotherapy, but said methods and compositions may also be used in the form of combination therapy in which one or more compounds of the invention are coadministered in combination with one or more additional therapeutic agents such as those described in detail further herein.

In a further embodiment of the invention, combinations of the present invention include treatment with a compound of formula (I), or a pharmaceutically acceptable salt, solvate or derivative thereof, and one or more additional therapeutic agents selected from the following: HIV protease inhibitors (PIs), including but not limited to indinavir, ritonavir, saquinavir, nelfinavir, lopinavir, amprenavir, atazanavir, tipranavir, AG1859 and TMC 114; non-nucleoside reverse transcriptase inhibitors (NNRTIs), including but not limited to nevirapine, delavirdine, capravirine, efavirenz, GW-8248, GW-5634 and TMC125; nucleoside/nucleotide reverse transcriptase inhibitors, including but not limited to zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, adefovir dipivoxil, tenofovir and emtricitabine; CCR5 antagonists, including but not limited to:

N-{(1S)-3-[3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-*exo*-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}-4,4-difluorocyclohexanecarboxamide or a pharmaceutically acceptable salt, solvate or derivative thereof,

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methyl 1-*endo*-{8-[(3*S*)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-1,4,6,7-tetrahydro-5*H*-imidazo[4,5-*c*]pyridine-5-carboxylate or a pharmaceutically acceptable salt, solvate or derivative thereof,

ethyl 1-*endo*-{8-[(3S)-3-(acetylamino)-3-(3-fluorophenyl)propyl]-8-azabicyclo[3.2.1]oct-3-yl}-2-methyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-c]pyridine-5-carboxylate or a pharmaceutically acceptable salt, solvate or derivative thereof, Sch-D, ONO-4128, AMD-887, GW-873140 and CMPD-167; integrase inhibitors, including but not limited to L-870,810; entry (e.g. fusion) inhibitors, including but not limited to enfuviritide; agents which inhibit the interaction of gp120 and CD4, including but not limited to BMS806 and BMS-488043; and RNaseH inhibitors.

There is also included within the scope the present invention, combinations of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or derivative thereof, together with one or more additional therapeutic agents independently selected from the group consisting of proliferation inhibitors, e.g. hydroxyurea; immunomodulators, such as granulocyte macrophage colony stimulating growth factors (e.g. sargramostim), and various forms of interferon or interferon derivatives; other chemokine receptor agonists/antagonists such as CXCR4 antagonists, e.g. AMD-070; tachykinin receptor modulators (e.g. NK1 antagonists) and various forms of interferon or interferon derivatives; inhibitors of viral transcription and RNA replication; agents which influence, in particular down regulate, CCR5 receptor expression; chemokines that induce CCR5 receptor internalisation such MIP-1α, MIP-1β, RANTES and derivatives thereof; and other agents that inhibit viral infection or improve the condition or outcome of HIV-infected individuals through different mechanisms.

Agents which influence (in particular down regulate) CCR5 receptor expression include immunosupressants, such as calcineurin inhibitors (e.g. tacrolimus and cyclosporin A); steroids; agents which interfere with cytokine production or signalling, such as Janus Kinase (JAK) inhibitors (e.g. JAK-3 inhibitors, including 3-{(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile) and pharmaceutically acceptable salts, solvates or derivatives thereof; cytokine antibodies (e.g. antibodies that inhibit the interleukin-2 (IL-2) receptor, including basiliximab and daclizumab); and agents which interfere with cell activation or cell cycling, such as rapamycin.

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There is also included within the scope the present invention, combinations of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or derivative thereof, together with one or more additional therapeutic agents which yet further slow down the rate of metabolism of the compound of the invention, thereby leading to increased exposure in patients. Increasing the exposure in such a manner is known as boosting. This has the benefit of increasing the efficacy of the compound of the invention or reducing the dose required to achieve the same efficacy as an unboosted dose. The metabolism of the compounds of the invention includes oxidative processes carried out by P450 (CYP450) enzymes, particularly CYP 3A4 and conjugation by UDP glucuronosyl transferase and sulphating enzymes. Thus, among the agents that may be used to increase the exposure of a patient to a compound of the present invention are those that can act as inhibitors of at least one isoform of the cytochrome P450 (CYP450) enzymes. The isoforms of CYP450 that may be beneficially inhibited include, but are not limited to, CYP1A2, CYP2D6, CYP2C9, CYP2C19 and CYP3A4. Suitable agents that may be used to inhibit CYP 3A4 include, but are not limited to, ritonavir, saquinavir or ketoconazole.

It will be appreciated by a person skilled in the art, that a combination drug treatment, as described herein above, may comprise two or more compounds having the same, or different, mechanism of action. Thus, by way of illustration only, a combination may comprise a compound of the invention and: one or more other NNRTIs; one or more NRTIs and a PI; one or more NRTIs and a CCR5 antagonist; a PI; a PI and an NNRTI; and so on.

In addition to the requirement of therapeutic efficacy, which may necessitate the use of therapeutic agents in addition to the compounds of the invention, there may be additional rationales which compel or highly recommend the use of a combination of a compound of the invention and another therapeutic agent, such as in the treatment of diseases or conditions which directly result from or indirectly accompany the basic or underlying disease or condition. For example, it may be necessary or at least desirable to treat Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), Human Papillomavirus (HPV), opportunistic infections (including bacterial and fungal infections), neoplasms, and other conditions which occur as the result of the immune-compromised state of the patient being treated. Other therapeutic agents may be used with the compounds of the invention, *e.g.*, in order to provide immune stimulation or to treat pain and inflammation which accompany the initial and fundamental HIV infection.

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Accordingly, therapeutic agents for use in combination with the compounds of formula (I) and their pharmaceutically acceptable salts, solvates and derivatives also include: interferons, pegylated interferons (e.g. peginterferon alfa-2a and peginterferon alfa-2b), lamivudine, ribavirin, and emtricitabine for the treatment of hepatitis; antifungals such as fluconazole, itraconazole, and voriconazole; antibacterials such as azithromycin and clarithromycin; interferons, daunorubicin, doxorubicin, and paclitaxel for the treatment of AIDS related Kaposi's sarcoma; and cidofovir, fomivirsen, foscarnet, ganciclovir and valcyte for the treatment of cytomegalovirus (CMV) retinitis.

Further combinations for use according to the invention include combination of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or derivative thereof with a CCR1 antagonist, such as BX-471; a beta adrenoceptor agonist, such as salmeterol; a corticosteroid agonist, such fluticasone propionate; a LTD4 antagonist, such as montelukast; a muscarinic antagonist, such as tiotropium bromide; a PDE4 inhibitor, such as cilomilast or roflumilast; a COX-2 inhibitor, such as celecoxib, valdecoxib or rofecoxib; an alpha-2-delta ligand, such as gabapentin or pregabalin; a beta-interferon, such as REBIF; a TNF receptor modulator, such as a TNF-alpha inhibitor (e.g. adalimumab); a HMG CoA reductase inhibitor, such as a statin (e.g. atorvastatin); or an immunosuppressant, such as cyclosporin or a macrolide such as tacrolimus.

In the above-described combinations, the compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof and other therapeutic agent(s) may be administered, in terms of dosage forms, either separately or in conjunction with each other; and in terms of their time of administration, either simultaneously or sequentially. Thus, the administration of one component agent may be prior to, concurrent with, or subsequent to the administration of the other component agent(s).

Accordingly, in a further aspect the invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof and one or more additional therapeutic agents.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

The invention is illustrated by the following Examples and Preparations in which the following further abbreviations may be used:
0.88 ammonia = concentrated ammonium hydroxide solution, 0.88 SG

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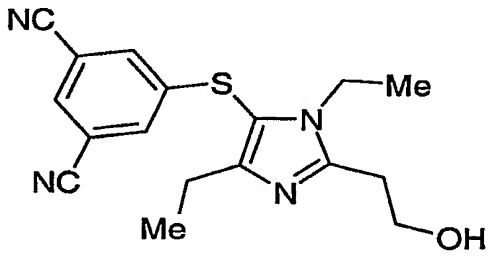
h = hour
min = minute
LRMS = low resolution mass spectrum
APCI+ = atmospheric pressure chemical ionisation
ESI+ = electrospray ionisation
LCMS = liquid chromatography-mass spectroscopy
Me = methyl
^{1}H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used: $CDCl_3$, deuterochloroform; D_6-DMSO, deuterodimethylsulphoxide; CD_3OD, deuteromethanol.
Liquid chromatography – mass spectroscopy (LCMS) conditions were:
Column: Phenomenex Luna 3u C18 100A, 50 x 2.00mm 3u Micron;
Eluent: 5min gradient method, Solvent A: 0.1% Formic Acid + Water, Solvent B: 0.1% Formic Acid + acetonitrile, 1ml/min.

Example 1

5-{[1,4-Diethyl-2-(2-hydroxyethyl)-1H-imidazol-5-yl]thio}isophthalonitrile



Ferric chloride (214mg, 1.3mmol) was added in one portion to a solution of 5-({2-[2-(benzyloxy)ethyl]-1,4-diethyl-1H-imidazol-5-yl}thio)isophthalonitrile (Preparation 8) (110mg, 0.26mmol) in dichloromethane (4mL), and the reaction stirred at room temperature for 10 minutes. After this time further ferric chloride (214mg, 1.3mmol) was added in one portion and the resulting mixture stirred at room temperature for 5 minutes. The mixture was diluted with ethyl acetate (20mL) and washed with saturated sodium bicarbonate solution (20mL). The layers were separated and the aqueous layer was washed with ethyl acetate (2 x 20mL). The combined organic solution was washed with water (10mL) then saturated brine (10mL), dried over

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magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using dichloromethane:methanol:0.88 ammonia (93:7:0.7). This afforded impure title compound as a yellow solid which was subjected to a second round of silica gel chromatography using an elution gradient of n-pentane:ethyl acetate (1:1 to 1:2), then an elution gradient of methanol:ethyl acetate (5:95) to afford the title compound as a colourless foam (32mg).

^{1}H NMR (400MHz, $CDCl_3$): δ 1.20 (m, 6H), 2.61 (q, 2H), 2.93 (t, 2H), 3.88 (q, 2H), 4.12 (t, 2H), 7.39 (s, 2H), 7.65 (s, 1H).

LRMS: *m/z* APCI 327 $[M+H]^+$.

Examples 2 and 3 in the following table (5-{[4-ethyl-2-(2-hydroxyethyl)-1-(pyridin-2-ylmethyl)-1H-imidazol-5-yl]thio}isophthalonitrile and 5-{[4-ethyl-2-(2-hydroxyethyl)-1-methyl-1H-imidazol-5-yl]thio}isophthalonitrile respectively) were prepared according to the method described above for Example 1 using the ethers of Preparations 9 and 10 respectively.

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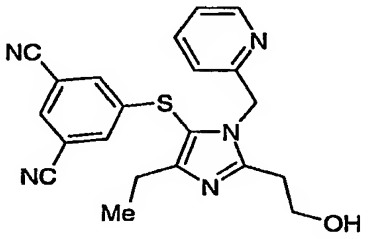
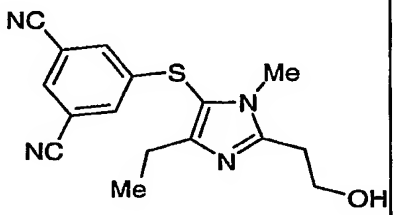
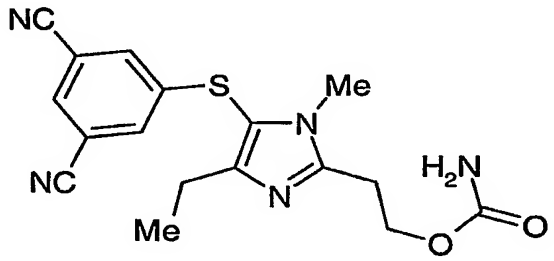
Example Number	Structure	LCMS	Analytical data
2		Retention time = 2.21 min. *m/z* ESI 390 $[M+H]^+$	^{1}H NMR (400MHz, D_6-DMSO): δ 1.08 (m, 3H), 2.49 (m, 2H), 2.89 (t, 2H), 3.74 (m, 2H), 4.81 (m, 1H), 5.28 (s, 2H), 7.08 (d, 1H), 7.14 (t, 1H), 7.45 (s, 2H), 7.53 (t, 1H), 8.06 (s,1H), 8.34 (d, 1H).
3		Retention time = 1.95 min. *m/z* ESI 313 $[M+H]^+$	^{1}H NMR (400MHz, D_6-DMSO): δ 1.05 (t, 3H), 2.48 (m, 2H), 2.85 (t, 2H), 3.32 (s, 3H), 3.72 (m, 2H), 4.78 (t, 1H), 7.69 (s, 2H), 8.23 (s, 1H).

Example 4

2-{5-[(3,5-Dicyanophenyl)thio]-4-ethyl-1-methyl-1H-imidazol-2-yl}ethyl carbamate



A solution of 5-{[1-methyl-4-ethyl-2-(2-hydroxyethyl)-1H-imidazol-5-yl]thio}isophthalonitrile (Example 3) (200mg 0.67mmol) was dissolved in dichloromethane (6mL) and treated, at 0°C, with trichloroacetylisocyanate (79μL, 0.67mmol). After stirring this mixture for 2 hours at 0°C, trichloroacetylisocyanate (79μL, 0.67mmol) was added and the reaction mixture stirred for 10 minutes before pouring onto a pad of alumina (Brockmann I, neutral alumina treated with 3% w/w water

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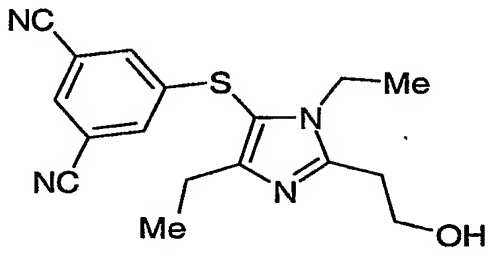
and stirred for 4 days). After ten minutes ethyl acetate (70mL) was passed through the pad of alumina and the filtrate evaporated to dryness to give a clear oil (223mg) that solidified upon standing. This residue was partitioned between ethyl acetate (50mL) and Na_2CO_3 (10% w/v aqueous solution, 50mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (50mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was recrystallised from ethyl acetate (20mL) to yield the title compound (89mg) as a white solid.

^{1}H NMR (400MHz, CD_3OD): δ 1.15 (t, 3H), 2.62 (q, 2H), 3.13 (t, 2H), 3.56 (s, 3H), 4.37 (t, 2H), 7.60 (s, 2H), 7.93 (s, 1H).

LCMS: Retention time = 2.37 min. *m/z* ESI 356 $[M+H]^+$

Example 5

5-{[1,4-Diethyl-2-(2-hydroxyethyl)-1H-imidazol-5-yl]thio}isophthalonitrile



To a solution of 5-({2-[2-(benzyloxy)ethyl]-1,4-diethyl-1H-imidazol-5-yl}thio)isophthalonitrile (Preparation 8) (65g 156 mmol) in dichloromethane (800mL) was added a solution of boron trichloride-methylsulphide complex in dichloromethane (156ml of a 2M solution, 312 mmol), dropwise, with stirring, over 25 minutes. The resulting solution was stirred at room temperature for 3 hours and then poured into saturated aqueous sodium bicarbonate solution (1L). The layers were separated and the aqueous layer was further extracted with dichloromethane (3 x 200mL). The combined organic fraction was washed with saturated brine (800mL) and dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using an elution gradient of methanol:ethyl acetate (0:1 to 1:10) to afford a solid. This solid was recrystallised from a mixture of ethyl acetate and pentane to afford the title compound as a white

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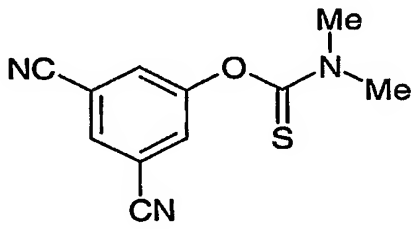
solid (28g). The ^{1}H NMR and LRMS data was identical to that for the title compound of Example 1.

Preparation 1

O-(3,5-Dicyanophenyl) dimethylthiocarbamate

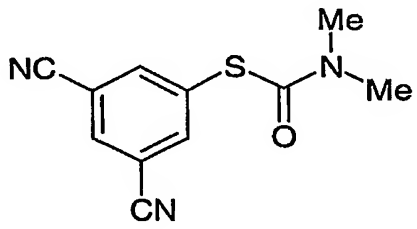


3,5-Dicyanohydroxybenzene (WO02/085860) (50g, 350 mmol) in 1-methyl-2-pyrrolidinone (200mL) was added to a stirred suspension of sodium carbonate (48g, 450mmol) in 1-methyl-2-pyrrolidinone (200mL) at 0°C under a nitrogen atmosphere. After warming to room temperature, the resulting mixture was stirred at ambient temperature for 30 minutes. Then a solution of dimethylthiocarbamoyl chloride (56g, 450mmol) in 1-methyl-2-pyrrolidinone (200mL) was added. The reaction mixture was stirred at room temperature for 30 minutes, then at 70°C for 16 hours. After this time, the reaction mixture was cooled to room temperature and water (200mL) was added. The resultant white precipitate was collected by filtration and dried in a vacuum oven at 55°C for 48 hours to give the title compound as a colourless solid (53g).

^{1}H NMR (400MHz, $CDCl_3$): δ 3.37 (s, 3H), 3.45 (s, 3H), 7.61 (s, 2H), 7.81 (s, 1H).

Preparation 2

S-(3,5-Dicyanophenyl) dimethylthiocarbamate



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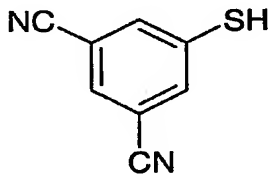
A sample of O-(3,5-Dicyanophenyl) dimethylthiocarbamate (Preparation 1) (49.9g, 216mmol) was heated at 200°C under a nitrogen atmosphere. The sample melted, started to blacken and after 1 hour solidified. Heating of this solid was continued for a further 2 hours and then the reaction mixture was allowed to cool to room temperature and was used directly in Preparation 3 without characterisation.

Preparation 3

5-Mercaptoisophthalonitrile



To a stirred suspension of S-(3,5-Dicyanophenyl) dimethylthiocarbamate (ex Preparation 2) in tetrahydrofuran (500mL) and methanol (400mL) at room temperature was added dropwise a solution of sodium hydroxide (8.6g, 216mmol) in methanol (100mL). After 15 hours the reaction mixture was concentrated and the residue was dissolved in water (800mL) and was washed with dichloromethane (2x100mL), before addition of 2M aqueous hydrochloric acid (110mL) to the aqueous component which resulted in a cream precipitate from a yellow solution. The precipitate was collected by filtration, washed with water (100mL) and dried by suction to give a beige powder. The crude product was recrystallised from methanol/water (approximately 1:1 by volume) to give an initial batch of the title compound as beige needles (10g). A second batch of the title compound was obtained by dilution of the mother liquors with water to give a white powder, suitable for recrystallisation as described above.

LRMS: *m/z* APCI 159 $[M-H]^+$.

Preparation 4

2-[2-(Benzyloxy)ethyl]-4-ethyl-1H-imidazole

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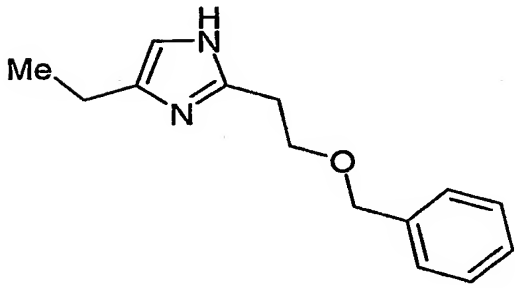
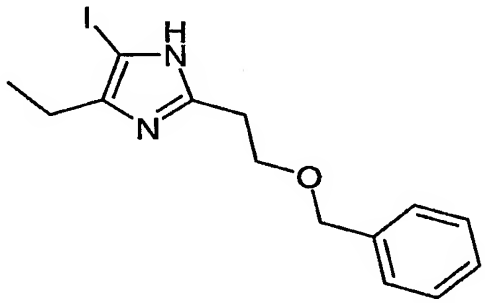


3-Benzyloxy-1-propionaldehyde (Tetrahedron, 2000, 56, 5303-5310) (2.82g, 17.5mmol) was added to a stirred solution of 2,2-dichlorobutanal (Synthesis, 1975, 455-456) (2.47g, 17.5mmol) in acetonitrile (10mL) at 0°C under a nitrogen atmosphere, followed by 0.88 ammonia (20mL). The reaction was stirred at room temperature for 16 hours. The mixture was evaporated under reduced pressure and the residual liquid was diluted with water (10mL), washed with dichloromethane (3 x 20mL), and the combined organic fraction was dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 98:2 to 97:3). This afforded the title compound as a yellow oil (1.84g).
LRMS: *m/z* APCI 231 $[M+H]^+$

Preparation 5

2-[2-(Benzyloxy)ethyl]-4-ethyl-5-iodo-1H-imidazole



To 2-[2-(Benzyloxy)ethyl]-4-ethyl-1H-imidazole (Preparation 4) (500mg, 2.17mmol) in dichloromethane (2.5mL) at 0°C was added a solution of sodium hydroxide (9.6mg, 2.4mmol) in water (1.5mL). A solution of iodine (716mg, 2.82mmol) in a mixture of dichloromethane and methanol (5:2, 6mL total) was added dropwise over 10 minutes to the vigorously stirred solution. The resulting mixture was stirred at 0°C for 20 minutes after which time the reaction was quenched with the addition of a 5% aqueous sodium sulphite

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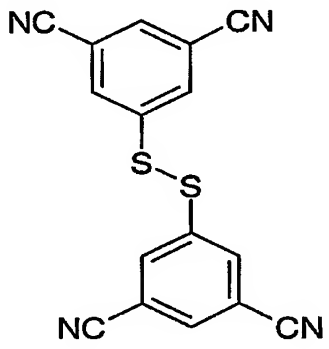
solution (40mL) and the mixture was extracted with dichloromethane (3 x 30mL). The combined organic fraction was washed with water (15mL) followed by a solution of brine (20mL), the organic fraction was dried over sodium sulphate, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using an elution gradient of dichloromethane:methanol:0.88 ammonia (100:0:0 to 95:5:0.5). This afforded the title compound as a colourless gum (460mg).
LRMS: *m/z* APCI 357 $[M+H]^+$.

Preparation 6

5-[(3,5-Dicyanophenyl)dithio]isophthalonitrile



To 5-Mercaptoisophthalonitrile (Preparation 3) (2 g, 12.5 mmol), suspended in a solution of potassium hydroxide (580 mg, 12.5 mmol) in water (4 mL), was added, dropwise, a solution of iodine (1.59 g, 6.25 mmol) and potassium iodide (2.07 g, 12.5 mmol) in water (4 mL). The resulting mixture was stirred at room temperature for 16 hours. The resulting solid which formed was collected by filtration and washed with water (10 mL). The wet solid was dissolved in ethyl acetate (300 mL), dried over magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel using an elution gradient of dichloromethane:ethyl acetate (100:0 to 95:5). This afforded the title compound as a white solid (800 mg).
^{1}H NMR (400MHz, $CDCl_3$): δ 7.85 (s, 2H), 7.95 (s, 4H).

Preparation 7

5-({2-[2-(Benzyloxy)ethyl]-4-ethyl-1H-imidazol-5-yl}thio)isophthalonitrile

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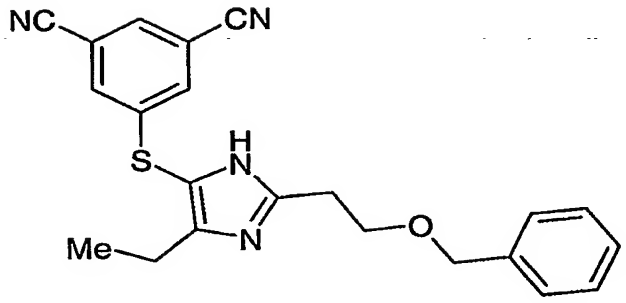
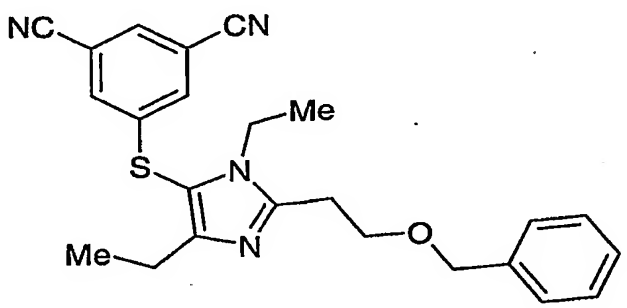


To 2-[2-(Benzyloxy)ethyl]-4-ethyl-5-iodo-1H-imidazole (Preparation 5 or 11) (450mg, 1.26mmol) in dry dimethylsulphoxide (2mL) was added lithium hydride in one portion (11mg, 1.35mmol). The resulting mixture was stirred under a nitrogen atmosphere for 10 minutes, after which time 5-[(3,5-Dicyanophenyl)dithio]isophthalonitrile (Preparation 6) was added in one portion (403mg 1.26mmol). The resulting solution was heated at 60°C for 3 hours and then cooled to room temperature. The mixture was then cooled to 0°C and water (40mL) added. The mixture was extracted with a mixture of ethyl acetate:diethyl ether (1:1, 2 x 50mL). The combined organic fraction was washed with water (15mL), followed by a solution of brine (2 x 30mL), dried over magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel using an elution gradient of dichloromethane:methanol (100:0 to 98:2). This afforded the title compound as an impure yellow oil which was subjected to a second round of silica gel chromatography using an elution gradient of n-pentane:ethyl acetate (1:1 to 1:4) to afford the title compound as a colourless gum (300mg).

LRMS: *m/z* APCI 389 $[M+H]^+$.

Preparation 8

5-({2-[2-(benzyloxy)ethyl]-1,4-diethyl-1H-imidazol-5-yl}thio)isophthalonitrile



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To 5-({2-[2-(benzyloxy)ethyl]-4-ethyl-1H-imidazol-5-yl}thio)isophthalonitrile (Preparation 7 or 12) (290 mg, 0.75 mmol) in *N,N*-dimethylformamide (1 mL) was added potassium carbonate (160 mg, 1.2 mmol) followed by ethyl iodide (125 mg, 0.8 mmol) and the resulting mixture stirred at room temperature for 26 hours. After this time the mixture was diluted with water (25 mL) and the mixture extracted with ethyl acetate (2 x 25 mL). The combined organic fraction was washed with water (5 mL) followed by a solution of brine (10 mL), dried over sodium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel using an elution gradient of toluene:ethyl acetate (4:1 to 2:1). This afforded the title compound as the most polar isomer (eluted second from the column) as a colourless gum (120 mg).
LRMS: *m/z* ES+ 417 $[M+H]^+$.

The compounds of Preparation 9 and 10 in the following table were prepared according to the method described above from Preparation 8 using the appropriate alkylating agent.

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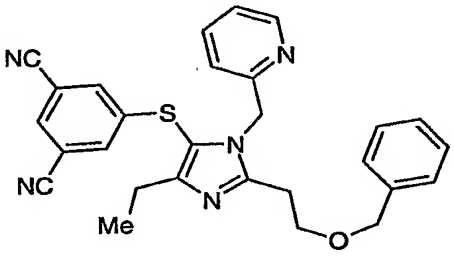
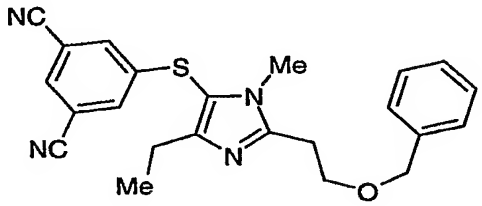
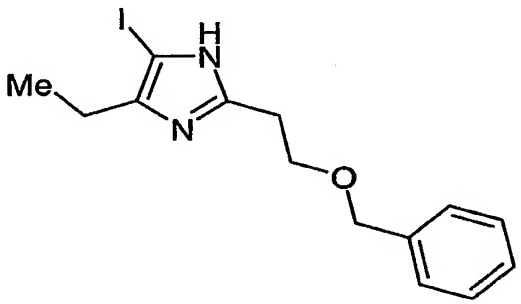
Preparation Number	Alkylating agent	Structure	LCMS
9	2-(Chloromethyl)-pyridine hydrochloride		Retention time = 2.93 min. *m/z* = 481 $[M+H]^+$
10	Iodomethane		Retention time = 2.66 min. *m/z* = 404 $[M+H]^+$

Preparation 11

2-[2-(Benzyloxy)ethyl]-4-ethyl-5-iodo-1H-imidazole



A solution of 3-benzyloxy-1-propionaldehyde (Tetrahedron, 2000, 56, 5303-5310) (135g, 957mmol) and 2,2-dichlorobutanal (Synthesis, 1975, 455-456) (154.3g, 957mmol) in acetonitrile (250mL) was cooled to -5°C under a nitrogen atmosphere and treated with 0.88 ammonia (650mL, added in 50mL portions). The reaction was stirred at room temperature for 16 hours. Dichloromethane (500mL) was added to the mixture and the layers separated. The aqueous layer was further extracted with dichloromethane (2

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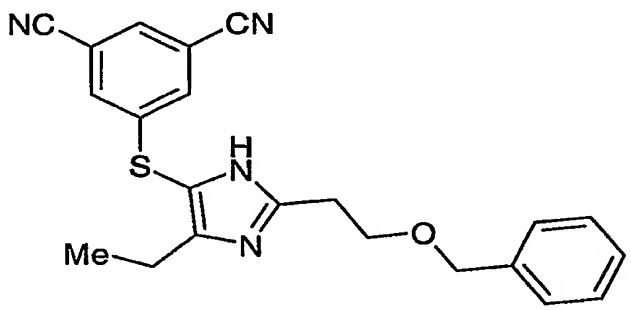
x 200mL) and the combined organic fraction was washed with saturated brine (500mL), dried over magnesium sulphate, filtered and evaporated under reduced pressure to give 244g of a thick orange oil. This oil was dissolved in dichloromethane (400mL), cooled to 0°C and treated with a solution of sodium hydroxide (46.61g, 1.165mol) in water (200mL). A slurry of iodine (295.8g, 1.165mol) in methanol:dichloromethane (1:1, 400mL) was then added to the well-stirred mixture. The resulting brown-black mixture was stirred for one hour and allowed to warm to 8°C. The mixture was diluted with dichloromethane (400mL) and treated with 10% aqueous sodium sulphite solution (500mL) with vigorous mixing. The layers were separated and the aqueous layer further extracted with dichloromethane (2 x 300mL). The combined organic fraction was washed with 10% aqueous sodium sulphite solution (500mL) and saturated brine (600mL), dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using an elution gradient of pentane:ethyl acetate (1:1 to 0:1) to give a solid. This solid was treated with pentane (1L), cooled and stirred; the resulting solid was collected by filtration and washed with pentane (500mL) to afford the title compound as a white solid (117.44g), the LRMS data for which was identical to that for the title compound of Preparation 5.

Preparation 12

5-({2-[2-(Benzyloxy)ethyl]-4-ethyl-1H-imidazol-5-yl}thio)isophthalonitrile



To 2-[2-(Benzyloxy)ethyl]-4-ethyl-5-iodo-1H-imidazole (Preparation 5 or 11) (18.5g, 51.97mmol) in acetonitrile (200mL) were added 5-mercaptoisophthalonitrile (Preparation 3) (6g, 72.5mmol) followed by caesium carbonate (13g, 77.85mmol). The resulting mixture was heated at reflux for 72 hours after which time the mixture was cooled to ambient temperature and water (150mL) added. To this was added dichloromethane

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(250mL) and the layers separated. The aqueous extract was washed with dichloromethane (150mL) and the combined organic extracts were washed with a solution of brine (150mL), dried over magnesium sulphate, filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate:pentane (1:1). This afforded the title compound as an orange oil (19.34g), the LRMS data for which was identical to the title compound of Preparation 7.

Biological data

The activity of the compounds of the invention as reverse transcriptase inhibitors may be measured using the following assay.

Inhibition of HIV-1 reverse transcriptase enzyme

The reverse transcriptase activity of the compounds of the invention may be assayed as follows. Using the purified recombinant HIV-1 reverse transcriptase (RT, EC, 2.7.7.49) obtained by expression in *Escherichia Coli*, a 384-well plate assay system was established for assaying a large number of samples using the [3H]-Flashplate enzyme assay system (NEN - SMP 410A) following the manufacturer's recommendations. The compounds were dissolved in 100% DMSO and diluted with the appropriate buffer to a 5% final DMSO concentration. The inhibitory activity was expressed in percent inhibition relative to the DMSO control. The concentration at which the compound inhibited the reverse transcriptase by 50% was expressed as the IC_{50} of the compound.

All the Examples of the invention have IC_{50} values, according to the above method, of less than 1.5μM. IC_{50} values for the compounds of Examples 1, and 4 are, respectively, 38nM, and 926nM.

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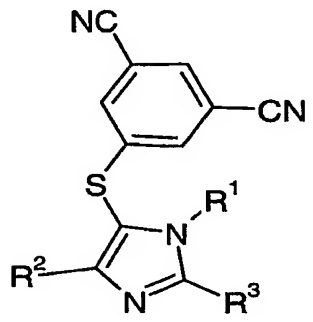
CLAIMS

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or derivative thereof, wherein:
R^1 is C_{1-4} alkyl or C_{3-6} cycloalkyl, wherein said alkyl is optionally substituted by pyridyl or pyridyl N-oxide;
R^2 is C_{1-4} alkyl, C_{3-6} cycloalkyl, or trifluoromethyl;
R^3 is $-(CH_2)_m OH$, $-(CH_2)_m OC(O)NH_2$, $-(CH_2)_m NH_2$, or $-(CH_2)_m NHC(O)NH_2$;
and m is 1, 2, 3 or 4.

2. A compound according to claim 1, wherein R^1 is methyl, ethyl, i-propyl, cyclopropyl, or pyridylmethyl.

3. A compound according to claim 1 or 2, wherein R^1 is methyl, ethyl or methylpyridyl.

4. A compound according to any preceding claim, wherein R^1 is methyl or ethyl.

5. A compound according to any preceding claim, wherein R^1 is ethyl.

6. A compound according to any preceding claim, wherein R^2 is methyl, ethyl, n-propyl, i-propyl, cyclopropyl, or trifluoromethyl.

7. A compound according to any preceding claim, wherein R^2 is ethyl, i-propyl or cyclopropyl.

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8. A compound according to any preceding claim, wherein R^2 is i-propyl or cyclopropyl.

9. A compound according to any preceding claim, wherein R^2 is ethyl.

10. A compound according to any preceding claim, wherein R^3 is $-(CH_2)_m OH$ or $-(CH_2)_m OC(O)NH_2$.

11. A compound according to any preceding claim, wherein R^3 is $-CH_2OH$, $-(CH_2)_2 OH$, $-CH_2OC(O)NH_2$ or $-(CH_2)_2OC(O)NH_2$.

12. A compound according to any preceding claim, wherein R^3 is $-CH_2OH$ or $-(CH_2)_2OH$.

13. A compound according to any preceding claim, wherein R^3 is $-(CH_2)_2OH$.

14. A compound according to any preceding claim, wherein R^3 is $-(CH_2)_2OC(O)NH_2$.

15. A pharmaceutical composition including a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof, according to any preceding claim, together with one or more pharmaceutically acceptable excipients, diluents or carriers.

16. A pharmaceutical composition according to claim 15 including one or more additional therapeutic agents.

17. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 15, or a pharmaceutical composition according to claim 14 or 16, for use as a medicament.

18. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 14, or a pharmaceutical composition according to claim 15 or 16, for use as a reverse transcriptase inhibitor or modulator.

19. A compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 14, or a

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pharmaceutical composition according to claim 15 or 16, for use in the treatment of an HIV, or genetically-related retroviral, infection or a resulting acquired immune deficiency syndrome (AIDS).

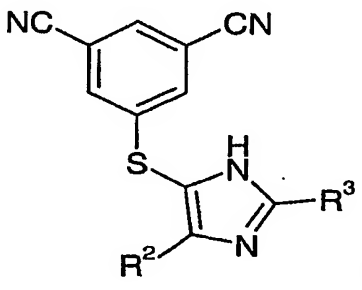
20. The use of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 14, or a pharmaceutical composition according to claim 15 or 16, for the manufacture of a medicament having reverse transcriptase inhibitory or modulating activity.

21. The use of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 14, or a pharmaceutical composition according to claim 15 or 16, for the manufacture of a medicament for the treatment of an HIV, or genetically-related retroviral, infection or a resulting acquired immune deficiency syndrome (AIDS).

22. A method of treatment of a mammal, including a human being, with a reverse transcriptase inhibitor or modulator including treating said mammal with an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 14, or a pharmaceutical composition according to claim 15 or 16.

23. A method of treatment of a mammal, including a human being, with an HIV, or genetically-related retroviral, infection or a resulting acquired immune deficiency syndrome (AIDS), including treating said mammal with an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof according to any of claims 1 to 14, or a pharmaceutical composition according to claim 15 or 16.

24. A process for preparing compounds of formula (I) comprising alkylation of a compound of formula (II)



(II)

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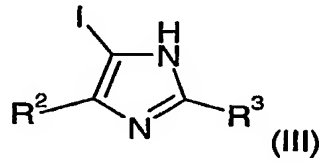
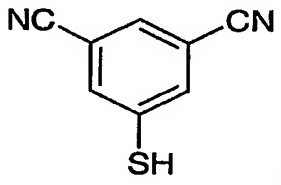
with R^1X, wherein R^1, R^2, R^3 and X are as defined above.

25. A process according to claim 24 wherein the preparation of a compound of formula (II) comprises reacting a compound of formula (III)



(III)

with a compound of formula (V)



(V)

in the presence of an alkali metal carbonate base.

26. A compound of formulae (II), (III) or (VI).

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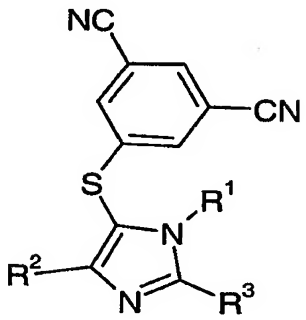
ABSTRACT

This invention relates to isophthalonitrile derivatives of formula (I)



(I)

or pharmaceutically acceptable salts, solvates or derivative thereof, wherein R^1 to R^3 are defined in the description, and to processes for the preparation thereof, intermediates used in their preparation of, compositions containing them and the uses of such derivatives.

The compounds of the present invention bind to the enzyme reverse transcriptase and are modulators, especially inhibitors thereof. As such the compounds of the present invention are useful in the treatment of a variety of disorders including those in which the inhibition of reverse transcriptase is implicated. Disorders of interest include those caused by Human Immunodificiency Virus (HIV) and genetically related retroviruses, such as Acquired Immune Deficiency Syndrome (AIDS).

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